General

Guideline Title

Guidelines on the diagnosis and management of Waldenström macroglobulinaemia.

Bibliographic Source(s)

Owen RG, Pratt G, Auer RL, Flatley R, Kyriakou C, Lunn MP, Matthey F, McCarthy H, McNicholl FP, Rassam SM, Wagner SD, Streetly M, D'Sa S, British Committee for Standards in Haematology. Guidelines on the diagnosis and management of WaldenstrÃ¶m macroglobulinaemia. Br J Haematol. 2014 May;165(3):316-33. [126 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Johnson SA, Birchall J, Luckie C, Oscier DG, Owen RG, Haemato-Oncology Task Force of the British Committee for Standards in Haematology. Guidelines on the management of Waldenstrom macroglobulinaemia. Br J Haematol. 2006 Mar;132(6):683-97. [108 references]

Recommendations

Major Recommendations

Definitions for the quality of evidence (A–C) and strength of recommendations (Strong [Grade 1], Weak [Grade 2]) are given at the end of the "Major Recommendations" field.

Epidemiology

1. Although there is emerging evidence for familial clustering in Waldenström macroglobulinaemia (WM), the absolute level of risk for first-degree relatives remains low and, in the absence of obvious clinical need, systematic screening of family members is not indicated (Grade B1).

Investigation and Diagnosis

Laboratory Assessment

1. Sequential monitoring of immunoglobulin M (IgM) should be performed in a single laboratory using a single methodology (Grade A1).
2. The value of serum free light chain (SFLC) and Hevylite™ chain (HLC) assays have not been established and are not essential for the routine assessment of WM patients (Grade C2).
3. Anti-myelin-associated glycoprotein (MAG) serology and nerve conduction studies are recommended in patients with symptomatic peripheral neuropathy (Grade A1).

4. Screening for hepatitis B virus (HBV) and hepatitis C virus (HCV) is required prior to the introduction of rituximab-containing treatments (Grade A1).

Bone Marrow Assessment

1. Bone marrow aspirate and trephine biopsy assessment along with appropriate immunophenotypic studies are required for a definitive diagnosis of WM (Grade A1).
2. In accordance with national guidance on diagnosis in haematological malignancies, all cases should be subject to formal central review (Grade A1).

Cytogenetic Analysis

1. Cytogenetic analysis is not required for the routine diagnostic assessment of WM patients (Grade B1).
2. Further evaluation of the prognostic significance of del (6q) and deletion of *TP53* are required, ideally in the context of prospective clinical trials (Grade B2).

Imaging

1. Baseline computed tomography (CT) scans (chest, abdomen, pelvis) are recommended in all symptomatic patients prior to the commencement of chemotherapy (Grade B1).
2. The value of fluoro-deoxyglucose positron emission tomography (FDG-PET) remains to be determined and is not recommended outside a clinical trial (Grade C2).

Histological Transformation

1. Tissue biopsy is recommended in all patients with suspected histological transformation. Detailed pathological assessment should include assessment of Epstein-Barr virus (EBV) by immunohistochemistry and/or *in situ* hybridization (Grade A1).

Prognostic Assessment

1. The international prognostic scoring system for WM (ISSWM) should be recorded in all patients at presentation (Grade A1) but there is no evidence to support its use in determining treatment approaches for individual patients (Grade B1).

Response Assessment

1. Treatment responses should be defined using the uniform response criteria (Grade A1).
2. Assessment of SFLC and HLC are not routinely required in the assessment of response (Grade C2).
3. Repeat bone marrow aspirate and trephine biopsies are encouraged to refine response assessment in individual patients (Grade A1).

Therapy for Waldenström Macroglobulinaemia

Choice of Primary Therapy in Symptomatic Individuals

1. Patients with symptomatic WM should receive a rituximab-containing regimen (Grade A1). Appropriate regimens include dexamethasone + rituximab + cyclophosphamide (DRC), bendamustine + rituximab (BR), fludarabine + rituximab (FR), fludarabine + cyclophosphamide + rituximab (FCR) and cladribine + rituximab (Clad-R). The choice of regimen in individual patients will take into consideration performance status, clinical features including renal function, co-morbidities and potential candidacy for stem cell transplantation (SCT) (Grade B1).
2. Given the risk of IgM flare, careful monitoring of all patients receiving rituximab is required with monitoring of sequential IgM, clinical assessment for hyperviscosity (HVS) and monitoring of plasma viscosity (PV) if available (Grade A1). The introduction of rituximab should be deferred in patients considered at a higher risk of HVS, this being arbitrarily defined by an IgM M-protein >40 g/l and/or a PV >4 centipoise (cP) (Grade C1).
3. Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisolone (CHOP-R) should not be used as primary therapy in WM (Grade B1).
4. Chlorambucil remains suitable therapy in elderly frail patients (Grade B1).
5. The use of bortezomib is not routinely recommended as primary therapy outside the context of a clinical trial (Grade B2).
6. There is insufficient evidence to support the use of maintenance rituximab (Grade C2).

Choice of Therapy at Relapse

1. Repeat bone marrow aspirate and trephine assessment and CT scanning should be performed prior to the reintroduction of treatment

(Grade B1).
2. Patients who remain asymptomatic despite serological evidence of progression can be observed until clinical symptoms occur (Grade A1).
3. Patients should receive a rituximab-containing regimen if CD20 is expressed. Appropriate regimens include FR, FCR, Clad-R, BR and DRC. The choice of regimen in individual patients will take into consideration performance status, clinical features including renal function, co-morbidities and potential candidacy for SCT (Grade B1).
4. Retreatment with primary therapy may be appropriate in some patients (Grade B1).
5. Bortezomib-containing regimens are suitable in the relapse setting. Weekly regimens are preferable, given the neurological toxicity associated with the biweekly schedules. Prophylaxis against herpes zoster virus (HZV) reactivation is recommended (Grade B1).
6. Alemtuzumab is a potential option in refractory disease (Grade B1). Surveillance for cytomegalovirus (CMV) reactivation is recommended.

Treatment for Histological Transformation

1. A diagnosis of transformation requires histological confirmation (Grade A1).
2. Patients who are suitable for intensive therapy should receive regimens currently employed for primary diffuse large B-cell lymphoma (DLBCL) (Grade B1).
3. Younger responding patients are candidates for an SCT procedure and should be discussed with a transplant centre (Grade B2).

Transplantation

1. Autologous SCT is a feasible therapeutic option for relapsed WM in younger, fitter patients with aggressive disease (short progression-free survival [PFS], histological transformation) (Grade B2).
2. Allogeneic SCT may be considered in selected younger patients with relapsed WM and aggressive clinical course (short PFS, histological transformation) (Grade B2).
3. Autologous and allogeneic SCT should only be performed in the setting of chemosensitive disease and at least a partial response (PR) to reinduction therapy (Grade A1).

Hyperviscosity Syndrome

1. Plasma exchange is recommended for all patients with HVS, irrespective of PV (Grade A1).
2. As per previous guidance, 1–2 procedures, exchanging 1–1.5 calculated plasma volumes, is advised (Grade A1).
3. Plasma exchange may be indicated in certain asymptomatic individuals, depending on the clinical circumstances, recorded plasma viscosities and co-morbidities (Grade C2).

IgM-Related Syndromes

Peripheral Neuropathy

1. Neurological examination should be performed in all patients with an IgM paraprotein (Grade A1).
2. Collaborative working with a neurologist is encouraged. Anti-MAG serology and nerve conduction studies are recommended in patients with symptomatic peripheral neuropathy (Grade A1).
3. Chemotherapeutic intervention should be considered in those patients with disabling or rapidly progressive anti-MAG neuropathy (Grade B1).
4. If chemotherapy is considered appropriate, a rituximab-containing regimen is appropriate with the final choice of regimen being determined by factors such as performance status, co-morbidities and renal function (Grade B1).

Cold Haemagglutinin Disease (CHAD)

1. Rituximab-based therapy is recommended for patients with symptomatic CHAD. The addition of fludarabine should be considered for patients with adequate performance status and renal function (Grade B1).

Cryoglobulinaemia

1. Cryoglobulinaemia should be considered in patients with IgM monoclonal gammopathy and unexplained purpura, arthralgia, haematuria or peripheral neuropathy (Grade A1).
2. Patients with cryoglobulinaemia should be screened for HCV infection (Grade A1).
3. Patients with symptomatic cryoglobulinaemia may be treated with corticosteroids and rituximab (Grade B1).
4. Patients with symptomatic cryoglobulinaemia and overt WM can be treated with standard therapies (Grade B1).

Supportive Care

1. Antimicrobial prophylaxis should be considered for patients with hypogammaglobulinaemia who develop recurrent bacterial infections (Grade B1).
2. Immunoglobulin replacement therapy should be according to the United Kingdom (UK) Department of Health clinical guidelines (Grade B1).
3. Anti-*Pneumocystis jirovecii* prophylaxis is recommended in patients requiring intensive and/or immunosuppressive treatment (Grade B1).
4. Anti-herpes simplex virus (HSV) and -HZV prophylaxis is recommended in patients requiring intensive, immunosuppressive or bortezomib-based therapy (Grade B1).
5. Pneumocystis and herpes prophylaxis is not routinely required in patients treated with alkylating agents or bendamustine (Grade B2).
6. The duration of anti-pneumocystis and herpes prophylaxis is controversial. Recommendations range from a minimum of 2 months post-therapy to awaiting a rise in CD4 count to 0.2 x 10^9/l (Grade C2).
7. Vaccination against *Streptococcus pneumoniae* (using a conjugate vaccine) and *Haemophilus influenzae* type B (HIB) is encouraged at diagnosis although there is a lack of randomized trials to support vaccination. Patients who respond to vaccination and subsequently develop recurrent bacterial infections should be revaccinated if *S. pneumoniae* and HIB antibody levels have fallen (Grade C1).
8. Annual vaccination against seasonal influenza including novel strains is recommended (Grade C1).
9. Live vaccines, such as polio, herpes zoster and yellow fever, should be avoided (Grade A1).
10. Vaccinations should be avoided, if possible, 2 weeks prior to, during and for 6 months after chemo-immunotherapy (Grade B1).

Definitions:

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context, it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Strength of Recommendations

Strong (Grade 1): Strong recommendations (Grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as "recommend".

Weak (Grade 2): Where the magnitude of benefit or not is less certain a weaker Grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as "suggest".

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Waldenström macroglobulinaemia

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Hematology

Neurology

Oncology

Intended Users

Physicians

Guideline Objective(s)

To provide guidelines for the diagnosis and management of patients with Waldenström macroglobulinaemia

Target Population

Patients with or suspected of having Waldenström macroglobulinaemia

Interventions and Practices Considered

Diagnosis/Evaluation

1. Sequential monitoring of immunoglobulin (Ig)M
2. Serum free light chain (SFLC) and Hevylite^{TM} chain (HLC) assays (not recommended routinely)
3. Anti-myelin-associated glycoprotein (MAG) serology
4. Nerve conduction studies
5. Screening for hepatitis B virus (HBV) and hepatitis C virus (HCV)
6. Bone marrow aspirate and trephine biopsy assessment with appropriate immunophenotypic studies
7. Formal central review of all cases
8. Cytogenetic analysis (not recommended routinely)
9. Evaluation of the prognostic significance of del (6q) and deletion of *TP53*
10. Baseline computerized tomography (CT) scans (chest, abdomen, pelvis)
11. Fluoro-deoxyglucose positron emission tomography (FDG-PET) (not recommended outside of clinical trials)
12. Systematic screening of family members for Waldenström macroglobulinaemia (WM) (not recommended)
13. Tissue biopsy in all patients with suspected histological transformation with detailed pathological assessment (Epstein-Barr virus by immunohistochemistry and/or *in situ* hybridization)
14. Use of international prognostic scoring system for WM (ISSWM)
15. Assessment of SFLC and HLC (not recommended routinely)
16. Use of uniform response criteria for treatment response
17. Repeat of bone marrow aspirate and trephine biopsies

Treatment/Management

1. Rituximab-containing regimens
2. Monitoring for IgM flare (monitoring of sequential IgM, clinical assessment of hyperviscosity [HVS, monitoring of plasma viscosity [PV])
3. Chlorambucil
4. Bortezomib (not recommended outside of clinical trials but suitable in the relapse setting)
5. Retreatment with primary therapy (for relapse)
6. Alemtuzumab in refractory disease
7. Surveillance for cytomegalovirus reactivation
8. Treatment for histological transformation using regimens currently employed for primary diffuse large B-cell lymphoma (DLBCL)
9. Autologous or allogeneic stem cell transplantation (SCT)
10. Plasma exchange for hyperviscosity syndrome
11. Neurological examination for and treatment of IgM-related neuropathy
12. Management of cold haemagglutinin disease (CHAD) and cryoglobulinaemia
13. Supportive care: antimicrobial prophylaxis, immunoglobulin replacement therapy, anti-*Pneumocystis jirovecii* prophylaxis, anti-herpes simplex virus (HSV) and –herpes zoster virus (HZV) prophylaxis, vaccinations against *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, and influenza

Major Outcomes Considered

- Response to therapy
- Adverse effects
- Quality of life
- Survival rate (5-year, progression-free, complete, overall)
- Overall response rate
- Treatment-related mortality

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

The production of these guidelines involved a systematic review of published English language literature up to July 2013 using MEDLINE and PubMed and including data presented in abstract form at the 2012 American Society of Hematology meeting. Search terms used were Waldenstroms macroglobulinaemia and lymphoplasmacytic lymphoma.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context, it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

These guidelines have been prepared using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) nomenclature for assessing the quality of evidence (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The guideline group was selected to be representative of UK experts in Waldenström macroglobulinaemia (WM). Recommendations are based on the systematic review of published English language literature. The writing group produced a draft guideline, which was reviewed and revised by members of the Haemato-Oncology Task Force of the British Committee for Standards in Haematology (BCSH).

These guidelines have been prepared using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) nomenclature for providing strength of recommendations (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (Grade 1): Strong recommendations (Grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as "recommend".

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Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was reviewed by a sounding board of approximately 50 United Kingdom haematologists and British Committee for Standards in Haematology (BCSH) and the British Society for Haematology Committee and further consensus amendments were made.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and management of Waldenström macroglobulinaemia

Potential Harms

- Rituximab dose reductions to avoid toxicity should be considered, particularly with the first course of treatment, with potential to increase the dose if well tolerated in some patients. Severely frail patients with a very poor performance status are unlikely to benefit from treatment.
- Despite the reported efficacy of the purine analogue rituximab combinations, doubts remain regarding their overall suitability in certain patients. There are concerns regarding their suitability in patients who may be potential candidates for autologous transplantation whilst concerns regarding myelotoxicity and infection are pertinent in elderly patients, particularly those with suboptimal renal function.
- Given the significant morbidity and mortality of the procedure, allogeneic transplantation can only be considered in selected younger, fitter patients with a good performance status and an aggressive but chemosensitive disease course.
- Treatment-related toxicity, including chemotherapy-associated myelotoxicity, infections, and neurotoxicity.
- Vaccinations should be avoided, if possible, 2 weeks prior to, during and for 6 months after chemo-immunotherapy.
- Live vaccines, such as polio, *H. zoster* and yellow fever, should be avoided.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Owen RG, Pratt G, Auer RL, Flatley R, Kyriakou C, Lunn MP, Matthey F, McCarthy H, McNicholl FP, Rassam SM, Wagner SD, Streetly M, D'Sa S, British Committee for Standards in Haematology. Guidelines on the diagnosis and management of WaldenstrÃ¶m macroglobulinaemia. Br J Haematol. 2014 May;165(3):316-33. [126 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2006 Mar (revised 2014 May)

Guideline Developer(s)

British Society for Haematology Guidelines - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

British Committee for Standards in Haematology (BCSH) Writing Group

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Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Johnson SA, Birchall J, Luckie C, Oscier DG, Owen RG, Haemato-Oncology Task Force of the British Committee for Standards in Haematology. Guidelines on the management of Waldenstrom macroglobulinaemia. Br J Haematol. 2006 Mar;132(6):683-97. [108 references]

Guideline Availability

Electronic copies: Available from the British Journal of Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on September 26, 2006. The information was verified by the guideline developer on October 25, 2006. This summary was updated by ECRI on January 12, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Rituxan (Rituximab). This summary was updated by ECRI Institute on October 8, 2008 following the U.S. Food and Drug Administration advisory on Rituxan (rituximab). This summary was updated by ECRI Institute on July 16, 2014. This summary was updated by ECRI Institute on March 19, 2015 following the U.S. Food and Drug Administration advisory on Treanda (bendamustine hydrochloride).

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